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LEWIS J. KREISLER
LEGAL DEPARTMENT
930 CLOPPER ROAD
GAITHERSBURG, MD 20878

EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,649	BELL ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7 and 9-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7 and 9-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-12-2005 +7-22-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on 7-12-2005 and the responses filed on 7-12-2005 and 7-15-2005 are acknowledged. Claims 1, 9-13 and 17 have been amended. Claims 2, 4-6 and 8 have been canceled. Claims 1, 3, 7 and 9-19 are pending and currently under examination.

Information Disclosure Statement

The Information Disclosure Statements filed on 7-12-2005 and 7-22-2005 have been considered. Initialed copies are attached hereto. It should be noted that not all of the cited references were available and consequently were not considered. Said references will be considered as they become available.

Claim Rejections Withdrawn

The rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "not a common human pathogen" is withdrawn in light of the amendment thereto.

The rejection of claim 2 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "substantially no PKR activity" is withdrawn. Cancellation of said claim has rendered the rejection moot.

The rejection of claims 1-19 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing VSV for reducing the viability of cell lines *in vitro* and the use of VSV to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization of any

virus other than VSV (that are not common human pathogens) for the reduction of viability of all types of melanoma tumor cells (either *in vivo* or *in vitro)* or the utilization of any virus to reduce the viability of a tumor cell in an immunocompetent animal is withdrawn in light of amendment thereto. A modified enablement rejection is set forth below.

Claim Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 1 and 4-6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 and 6-9 of copending Application No. 10/717,101 is maintained for reasons of record. Applicant indicates they will consider filing a terminal disclaimer when otherwise allowable subject matter is indicated.

As outlined previously, although the conflicting claims are not identical, they are not patentably distinct from each other because:

The claims of the instant application are drawn to methods of reducing the viability of a melanoma tumor cell comprising administering to said tumor cell a virus that is not a common

human pathogen wherein said virus is vesicular stomatitis virus (VSV). The claims of application 10/717,101 are drawn to a method of reducing or eliminating neoplastic cells *ex vivo* from a mixed population of cells wherein said method comprises contacting the cell population with a virus (i.e. VSV). Hence, both claim sets encompass the reduction of viability (killing/elimination) of tumor cells by the administration of VSV *ex vivo* (i.e. not within the body of an animal). It should be noted that while the claims of application 10/717,101 are drawn to all neoplastic cells and do not explicitly recite the use of melanoma tumor cells in the claimed method, their use was contemplated by the inventors (see paragraph 027 of the specification of application 10/717,101). The skilled artisan in order to practice the methods recited in the claims of application 10/717,101 would necessarily look to the specification to determine what cell types are encompassed by the term "neoplastic cells". Thus it would have been an obvious variation recited methods to use melanoma tumor cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1, 14-15 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Roberts et al. (WO 99/18799) is maintained for reasons of record. . The cancellation of claims 4-6 has rendered the rejection of those claims moot.

Applicant argues:

1. Said reference does not disclose an attenuated VSV.

Applicant's arguments have been fully considered and deemed non-persuasive.

Contrary to Applicant's assertion, Roberts et al. not only disclose the use of VSV but also disclose the creation of an attenuating mutation that results in lower virulence (see page 8, fifth paragraph). . Consequently, Roberts et al. anticipates all the limitations of the instant invention.

As outlined previously, Roberts et al. disclose methods utilizing oncolytic viruses to treat (kill) neoplasms wherein said treatment comprises contacting the neoplastic tumor cells with the virus (see abstract). Roberts et al. further disclose that the oncolytic virus can be vesicular stomatitis virus (see page 21 and Table 1) and that VSV was capable of tumor cell specific killing (i.e. VSV selectively infects tumor cells deficient in IFN responsiveness and not "normal" cells)[see page 26, first paragraph]. Moreover, Roberts et al. disclose that their methods could be used to treat melanomas (see page 30, last paragraph). Consequently, Roberts et al. anticipates all the limitations of the rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claim 16 rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (WO 99/18799 --IDS) in view of Molnar-Kimber et al. (WO99/45783 --IDS) is maintained for reasons of record.

Applicant argues:

1. Said references do not disclose an attenuated VSV.

Applicant's arguments have been fully considered and deemed non-persuasive.

Contrary to Applicant's assertion, Roberts et al. not only disclose the use of VSV but also disclose the creation of an attenuating mutation that results in lower virulence (see page 8, fifth paragraph).

As outlined previously, Roberts et al. disclose methods utilizing oncolytic viruses to treat (kill) neoplasms wherein said treatment comprises contacting the neoplastic tumor cells with the virus (see abstract). Roberts et al. further disclose that the oncolytic virus can be vesicular stomatitis virus (see page 21 and Table 1) and that VSV was capable of tumor cell specific

killing (i.e. VSV selectively infects tumor cells deficient in IFN responsiveness and not "normal" cells)[see page 26, first paragraph]. Moreover, Roberts et al. disclose that their methods could be used to treat melanomas (see page 30, last paragraph).

Roberts et al. differ from instant invention in that they do not disclose the use of cells (i.e. producer cells) for the delivery of the oncolytic virus.

Molnar-Kimber et al. disclose the use of producer cells for the delivery of oncolytic viruses to tumor cells (see abstract). Molnar-Kimber et al. further disclose that said producer cells could be used to deliver VSV to tumor cells (see page 15. lines 10-11). Moreover, Molnar-Kimber et al. disclose that the use of producer cells has many advantages over direct injection methods. Said advantages include: 1) the amount of virus which can be administered in a given volume of fluid can be greatly increased; 2) delivery of a virus within a producer cell may enable the virus to elude the subjects immune system; 3) use of producer cells with a binding affinity for the tumor cells would increase the localization of virus delivery (see page 8, line 24 to page 9, line 5).

Consequently, it would have been obvious to one of skill in the art to use producer cells, as disclosed by Molnar-Kimber et al., in the method of melanoma tumor cell treatment disclosed by Roberts et al. One would have been motivated to due so in order to receive the expected benefits associated with the use of producer cells, as taught by Molnar-Kimber et al. and cited above. One of ordinary skill in the art would necessarily have a reasonable expectation of success since both methods utilize VSV to treat tumor cells.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 9-13 under 35 U.S.C. 112, first paragraph, for failing to meet the biological deposit requirements is maintained for reasons of record.

Applicant argues:

1. A variety of researchers have had access to VSV mutant strains and therefore a deposit is not necessary.

2. Many scientific journals require their authors to agree to make biological materials available to the research community.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant has failed to demonstrate that the VSV strains designated M1, M2, M3, M4 and M5 are well known and readily available to the public. Moreover, Applicant's to references in the art to viruses with the same designations is insufficient to overcome the instant rejection as Applicant has failed to demonstrate that those viruses recited in the cited references constitute the same entities recited in the rejected claims.

As outlined previously, it is apparent that the VSV strains M1, M2, M3, M4 and M5 are required in order to practice the invention. The deposit of biological organisms is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF 1.808(a)).

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to

make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and

5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CRF 1.809(d) should be added to the specification. See 37 CFR 1.803 – 1.809 for additional explanation of these requirements.

New Grounds of Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 7 and 9-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing attenuated VSV for reducing the viability of cell lines *in vitro* and the use of attenuated VSV to reduce the viability of tumor cell

based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization attenuated VSV for the reduction of viability of all types of melanoma tumor cells (either *in vivo* or *in vitro)* or the utilization of said attenuated VSV to reduce the viability of a tumor cell in an immunocompetent animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant's arguments to the previous enablement rejection are addressed below to the degree they read on the new rejection and the amended claims.

Applicant argues:

1. The Office has improperly sought to place on Applicant the burden of proving that the invention works.

2. Applicant is not required to submit experimental results demonstrating the anti-tumor activity of VSV. Rather the Office must establish what the specification does not meet the enablement requirement.

3. No evidence or reasoning has bee cited in support of the rejection.

4. In addition to the specification, other sources support the claim that melanoma cancers are appropriate targets for VSV therapy.

5. A number of different classes of **melanoma cell lines** were tested both *in vitro* and *in vivo*

6. All or virtually all melanoma tumor cell types are susceptible to the anti-tumor effects of VSV hence there is no need for the specification to disclose which carcinoma "are susceptible".

7. The Office has improperly tried to place on Applicant the burden of proving *in vivo* efficacy.

8. Cell lines implanted into athymic mice are not only an acceptable model but also a standard by industry and the NCI for determining efficacy of a novel anticancer agent.

9. The FDA accepts positive tumor xenograft results as a sufficient level of preclinical activity when approving a clinical trial for an investigational new drug.

10. Since all five mutants disclosed in the specification (Example 20) were found to be selective at *in vitro* killing of tumor cells the *in vivo* testing of only two of them (Example 25) does not undermine the predictability of *in vivo* efficacy.

11. The Office is exceeding its mandate conferred by the patent laws when requiring Applicant to demonstrate that their invention "provides benefit".

12. The Office cites several references that merely demonstrate that the *in vivo* environment cannot be duplicated *in vitro*. However, *in vitro* experiments continue to be relied upon to identify treatments for *in vivo* use.

13. The *in vivo* activity of VSV has been demonstrated (Table 1 of response).

14. The Office improperly sought to place on Applicant the burden of explaining the mechanism by which the invention works.

15. Toxicity and efficacy are very different and independent endpoints. The lack of toxicity does not imply that there would be a lack of efficacy.

16. The results disclosed in the references cited in Table C of the response confirm the efficacy of VSV when given intravenously and intratumoral to solid tumors in mice.

17. The specification contains *in vivo* data demonstrating the efficacy of intravenous VSV in treating human melanoma xenografts in nude mice.

Applicant's arguments have been fully considered and deemed non-persuasive.

On the basis of experimentation performed using an animal model, the specification asserts the invention can be used to treat cancer (melanoma). The problem with accepting such an assertion lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer "vaccines" to attenuate cancer has been met with very little success. In addition to references cited in preceding Office actions, which also describe such disappointing results and attribute the lack of success to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290) reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

> Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunization can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

> Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs,

such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Moreover, as noted in preceding Office action, Gura (of record) teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

With further regard to the predictive value of various different preclinical models, Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Applicant has argued that the use of xenografts in mice for evaluating therapeutic efficacy of drugs for treating humans is well established; agreeably the model has been utilized, but its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen. Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations

towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotropic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The position of the Office is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the

claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

With regard to Points 1-2 and 7, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). **The MPEP further states that physiological activity can be considered inherently unpredictable.** Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

With regard to Point 3, multiple references were (are) cited in support of the Office's positions (see above and below).

With regard to Points 4, the cited references may disclose that melanoma cancers may be an attractive target for VSV, they do not provide support for the *in vivo* treatment of melanomas in any animal other than a mouse.

With regard to Points 5 and 8, the ability to treat cell lines *in vitro* and xenografts *in vivo* (in mice) does not correlate to efficacy for the *in vivo* treatment of carcinomas in any animal other than a mouse (see above).

With regard to Point 6, Applicant has provided no evidence that **all or virtually all melanoma cell types** are susceptible to the anti-tumor effects VSV.

With regard to Point 9, while the FDA may rely on xenograft results to determining whether to approve a clinical trial, it is the clinical trials that determines whether a given treatment modality has efficacy *in vivo*. As outlined above, many treatment modalities that have been effective against xenografts proved to have no efficacy *in vivo*.

With regard to Point 10, even if all five mutants were shown to have efficacy against xenografts in mice that doesn't correlate to *in vivo* efficacy against all carcinomas nor does it correlate to *in vivo* efficacy in any animal other than a mouse.

With regard to Point 11, enablement of treatment methods requires a demonstration of efficacy that correlates to demonstration of "providing a benefit".

With regard to Point 12, the cited references not only demonstrate that the *in vivo* environment cannot be duplicated *in vitro*, said references also demonstrate that limitations of xenograft based models and the lack of correlation between the efficacy in said models and *in vivo* efficacy in animals other than a mouse.

With regard to Point 13, Applicant has demonstrated the efficacy of treating xenografts with VSV in mice; this does not correlate to *in vivo* efficacy for the treatment of all melanomas in all animals (including man).

With regard to Point 14, Applicant is not required to explain the mechanism of action with regard to the anti-tumor effect of VSV. The lack of disclosure with regard to the receptors used by VSV was pointed out to illustrate that one would not know what cell types VSV could infect thus contributing the unpredictability of the claimed invention.

With regard to Point 15, while the lack of toxicity does not imply there would be a lack of efficacy, high toxicity (i.e. lethal toxicity) is indicative of a lack of efficacy (as is the case with the intravenous administration of VSV to PKR-/- mice.

With regard to Points 16 and 17, while the results disclosed in the specification and the references cited in Table C may demonstrate the ability of VSV, when administered intravenously, to treat injected cell lines and xenografts in mice, such data does not correlate to correlate to *in vivo* efficacy for the treatment of all melanomas in all animals (including man).

As outlined previously, enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be

considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of reducing the viability of melanoma tumor cells by administering an attenuated strain of VSV to said melanoma tumor cells. Said melanoma tumor cells can optionally be lung carcinoma cells (claim 2), have no PKR activity and/or have no STAT1 activity (claim 3). Said VSV virus can be unable to inactivate tumor cell PKR activity (claims 7 and 18), or may constitute strains M1-M5 (claims 9-13, respectively). Said method may be drawn to methods of "treating" tumor cells which reside in a mammalian host (claims 14-19). Said virus may be administered to the mammalian subject via virally infected cells (claim 16) or the direct administration of VSV (claim 17) with the optional administration of interferon prior to the administration of the virus (claim 19).

Breadth of the claims: The claims are extremely broad in that they encompass literally any attenuated VSV strain. Moreover, claims 14-19 are specifically drawn to the *in vivo* application of the claimed methods (i.e. treatment of a melanoma tumor cell within an animal) while claims 1, 2, 4, 8 and 10-14 encompass both *in vivo* and *in vitro* applications. It should be noted that all the instant claims read on the *in vivo* treatment of melanoma tumor cells in humans.

Guidance of the specification/The existence of working examples: To use the invention as claimed one must be able to differentially infect a susceptible tumor cell resulting in a reduction in said cell's viability. While the specification provides great detail on the susceptibility of different cell types to VSV and the protective effect of alpha interferon against

VSV infection, the specification is silent on the what viruses, other than VSV would induce the claimed anti-tumor effect. Additionally, the instant claims are drawn to all forms of melanoma tumor cells, while the specification has demonstrated only a single melanoma cell line (SK-MEL3) that is susceptible to VSV infection. (see Table 1 and page 28 of the specification) and said melanoma cell line was shown to be rapidly destroyed by VSV infection *in vitro* (see Table 2 and page 28 of the specification). The specification is silent on what receptor is utilized by VSV (or any other virus) for cell entry or which cell types would be able to support a productive viral infection making it difficult to determine if a given tumor cell would be susceptible to the oncolytic properties of VSV or be used as a suitable delivery vehicle. Moreover, the specification is equally silent on what other melanoma tumor cell types are killed by VSV infection. The invention seems to be predicated on the susceptible tumor cells lacking PKR activity, but the specification is silent on which melanoma tumor cells lack said function. Claims 15-19 are specifically drawn to the *in vivo* application of the claimed methods while claims 1-14 encompass both in *vivo* and *in vitro* applications.

State of the art: At the time of applicants' invention the art of using oncolytic viruses to treat melanomas was underdeveloped. While the use of oncolytic viruses has been known in the art for decades, said oncolytic viruses were limited, to viruses that would be considered human pathogens.

Predictability of the art and the amount of experimentation necessary:

People of skill in the art require evidence that a benefit can be derived by the therapeutic application of a given substance; however, a survey of the relevant art does not indicate that substances such as those claimed provide such benefit. The instant specification fails to provide significant direction on which viruses, if any, are capable of eliciting a therapeutic response (tumor cell death) when administered to an immunocompetent subject in need. Moreover, the specification is equally silent on how said viruses are to be administered to said subject. Jain discloses known barriers to the delivery of drugs into solid tumors (Scientific American Vol. 271 No. 1, pages 58-65, July 1994). Impediments to drug delivery include: (1) Non-uniform blood delivery to all areas of the rumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61) and (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1). Consequently, the method of administration would vary depending on the tumor cell type and location of said tumor. Unfortunately, the specification fails to provide guidance to how a given virus should be administered when treating a given carcinoma. The specification illustrates this point on page 33 where it states that PKR-/- mice were killed with VSV by several routes of infection but that these mice were not affected by intravenous injections of the virus. Moreover, there is a marked difference in the efficacy of delivering a therapeutic agent to a solid tumor cell as opposed to a leukemia cell.

The specification teaches how to use VSV to reduce the viability of melanoma cell lines injected into immunodeficient mice to form xenographs and provides *in vitro* data showing

effects of VSV infection on a single melanoma cell line (either with or without alpha interferon). However, the specification does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to "treat" carcinoma tumor cells, although *in vivo* use is clearly encompassed by the claims. Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* and xenograft data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed viruses as pharmaceuticals without undue experimentation. Moreover, while those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without

this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro)*. Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature 'for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Additionally, it should be noted that Example 25 is insufficient to provide enablement for the full breadth of the instant claims. Firstly, the xenographs utilized in Example 25 (on page 50 of the specification), comprise a melanoma derived cell line (SK-MEL3). Secondly, said example only utilizes two of the five VSV mutants disclosed in the instant specification suggesting that the anti-tumor effect of the disclosed VSV mutants is unpredictable. Thirdly, the instant claims are drawn to use of VSV to reduce the viability of all types of melanoma tumor cells whereas Example 25 demonstrates only that two mutated VSV viruses can reduce the viability of cell-line based xenographs in immunodeficient mice. This cannot be extrapolated to the use of wild-type (non-mutated) VSV against established tumors in an immunocompetent

animal. Gura (Science, Vol. 278, 1997 pages 1041-1042) teach that xenographs are not good models for determining the efficacy of a treatment modality since "xenograft tumors don't behave like naturally occurring tumors in humans" (see column 2). Gura illustrates the lack of correlation between efficacy in xenograft model systems and in vivo efficacy in humans when she states that the use of xenografts led them to discover "compounds that were good mouse drugs rather than good human drugs" (see the bottom of column 2 on page 1041).

Consequently, the specification while being enabling for methods utilizing VSV for reducing the viability of cell lines *in vitro* and the use of VSV to reduce the viability of tumor cell based xenografts in immunodeficient mice, does not reasonably provide enablement for the utilization VSV for the reduction of viability of all types of melanoma tumor cells (either *in vivo* or *in vitro)* or the utilization of any virus to reduce the viability of a melanoma tumor cell in an immunocompetent animal. The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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ROBERT A. ZEMAN
PRIMARY EXAMINER

November 28, 2006